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Published in:
Neuroscience Letters

DOI:
10.1016/j.neulet.2020.134980

Publication date:
2020

Neuroscience Letters 729 (2020) 134980

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Review article

Matrix metalloproteinases shape the oligodendrocyte (niche) during development and upon demyelination

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ARTICLE INFO

Keywords:
Demyelination
Remyelination
Extracellular matrix
Matrix metalloproteinase
Oligodendrocyte progenitor cell
Multiple sclerosis

ABSTRACT

The oligodendrocyte lineage cell is crucial to proper brain function. During central nervous system development, oligodendrocyte progenitor cells (OPCs) migrate and proliferate to populate the entire brain and spinal cord, and subsequently differentiate into mature oligodendrocytes that wrap neuronal axons in an insulating myelin layer. When damage occurs to the myelin sheath, OPCs are activated and recruited to the demyelinated site, where they differentiate into oligodendrocytes that remyelinate the denuded axons. The process of OPC attraction and differentiation is influenced by a multitude of factors from the cell's niche. Matrix metalloproteinases (MMPs) are powerful and versatile enzymes that do not only degrade extracellular matrix proteins, but also cleave cell surface receptors, growth factors, signaling molecules, proteases and other precursor proteins, leading to their activation or degradation. MMPs are markedly upregulated during brain development and upon demyelinating injury, where their broad functions influence the behavior of neural progenitor cells (NPCs), OPCs and oligodendrocytes. In this review, we focus on the role of MMPs in (re)myelination. We will start out in the developing brain with describing the effects of MMPs on NPCs, OPCs and eventually oligodendrocytes. Then, we will outline their functions in oligodendrocyte process extension and developmental myelination. Finally, we will review their potential role in demyelination, describe their significance in remyelination and discuss the evidence for a role of MMPs in remyelination failure, focusing on multiple sclerosis. In conclusion, MMPs shape the oligodendrocyte (niche) both during development and upon demyelination, and thus are important players in directing the fate and behavior of oligodendrocyte lineage cells throughout their life cycle.

1. Introduction

A cell type that is crucial to proper function of the brain and spinal cord is the oligodendrocyte lineage cell. During central nervous system (CNS) development, oligodendrocytes wrap neuronal axons in an insulating myelin layer. The myelin sheath provides protection, trophic and metabolic support to the neuronal-axonal unit [1–3] and enables rapid communication between neurons by facilitating saltatory conduction, which improves the speed of electrical signals up to 100 fold [4]. Mature oligodendrocytes originate from oligodendrocyte progenitor cells (OPCs), which do not disappear upon the completion of CNS myelination. In the adult brain, 5–8 % of cells are OPCs that are evenly distributed, while clusters of OPCs also remain present in the subventricular zones [5]. If the myelin sheath gets damaged later in life the OPC pool [6], or possibly pre-existing mature oligodendrocytes [7,8], become activated, revert to a more immature state and remyelinate neuronal axons in the damaged area [9,10].

Differentiation of OPCs into (re)myelinating oligodendrocytes is a complex process that is influenced by a plethora of promoting and inhibitory factors present in the oligodendrocyte niche. The

Abbreviations: ADAM, A disintegrin and metalloproteinase; BBB, blood-brain barrier; CNP, cyclic nucleotide 3'-phosphohydrolase; CNS, central nervous system; CSPGs, chondroitin sulfate proteoglycans; CXCR4, chemokine receptor type 4; EAE, experimental autoimmune encephalitis; ECM, extracellular matrix; GAL3, galectin-3; GFAP, glial fibrillary acidic protein; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; ISP, intracellular sigma peptide; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MMP, matrix metalloproteinase; MOG, myelin oligodendrocyte protein; MS, multiple sclerosis; MT-MMP, membrane-type MMP; NAWM, normal-appearing white matter; NCAM, neural cell adhesion molecule; NF155, 155 kDa neurofascin; NG2, neuron-glial antigen 2; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; NPC, neural progenitor cell; OPC, oligodendrocyte progenitor cell; PAR1, protease-activated receptor 1; PDGFRα, platelet-derived growth factor receptor α PLP proteolipid protein; PSA-NCAM, polysialylated NCAM; SDF1α, stromal cell-derived factor 1α; TME, Theiler's murine encephalomyelitis

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https://doi.org/10.1016/j.neulet.2020.134980
Received 22 September 2019; Received in revised form 4 April 2020; Accepted 9 April 2020
Available online 19 April 2020

microenvironment of the oligodendrocyte lineage cell is made up of neighboring cells, astrocytes, microglia and neurons, together with the extracellular matrix (ECM) proteins and soluble factors they secrete. Astrocytes are the most prevalent cells of the CNS and are classically seen as 'supportive cells', which are important for metabolic support of neurons, synapse formation, blood brain barrier (BBB) integrity and deposition of ECM [11]. Microglia are the innate immune cells of the CNS. In response to damaging stimuli, microglia become rapidly activated and secrete cytokines and proteases to initiate a (protective) inflammatory response [12]. Central to this, an intricate network of interconnected neurons generates impulses, which are conducted *via* neuronal axons and collectively compose our actions, memories and thoughts. Neurons communicate with OPCs, *e.g.*, through surface proteins on neuronal axons, like neural cell adhesion molecule (NCAM), or by secreting soluble factors, such as adenosine [13]. Neuronal activity stimulates myelination, while a lack of electrical signaling, *e.g.*, after prolonged social isolation [14], reduces myelin sheath formation. Neighboring astrocytes and microglia secrete cytokines, growth factors and other signaling molecules that influence OPC behavior. Moreover, many components of the ECM, *i.e.*, the dynamic protein network surrounding and interacting with cells, influence OPC migration, proliferation and (re)myelination [15,16]. For example, fibronectin stimulates OPC migration and proliferation, but inhibits OPC differentiation [17–23], while chondroitin sulfate proteoglycans (CSPGs) negatively affect OPC migration, proliferation and differentiation [24–27]. It is crucial that all these ECM proteins are expressed and removed at the right moment to provide the appropriate cues for OPCs in every stage of their development. Moreover, when myelination-inhibiting ECM proteins such as CSPGs fail to be removed, *e.g.*, in multiple sclerosis (MS) lesions or following spinal cord injury, failure of remyelination may ensue [15].

Two groups of proteins that are mainly responsible for ECM remodeling are the matrix metalloproteinases (MMPs) and the A disintegrin and metalloproteinases (ADAMs). MMPs are a family of at least 25 enzymes, which together are able to degrade all components of the ECM [28,29]. In recent years it has come to light that in addition to ECM proteins, MMPs cleave receptors, growth factors, signaling molecules, proteases and other precursor proteins, leading to their activation or degradation [30]. It is likely that MMPs play a major role both in developmental myelination and remyelination by remodeling, or failing to remodel, the extracellular landscape of the oligodendrocyte niche. However, only few studies focus on MMPs and make the connection between the presence or absence of aberrant ECM (and other) proteins and their degradation, or the lack thereof, by MMPs.

In this review, we focus on the role of MMPs in (re)myelination throughout the life cycle of oligodendrocyte lineage cells. We will start out in the developing brain with the effects of MMPs on migration of neural progenitor cells (NPCs) and their differentiation into OPCs and subsequently oligodendrocytes. Then, we will describe the functions of endogenously expressed and extracellularly provided MMPs in oligodendrocyte process extension and developmental myelination. Finally, we will detail the role of MMPs in demyelination, such as in Krabbe's disease, and describe the beneficial and detrimental effects of MMPs on remyelination, with a focus on MS. In all phases of oligodendrocyte development, MMPs shape the faith of the oligodendrocyte lineage cell by cleaving, degrading and activating a broad spectrum of proteins. New insights into the role of MMPs in oligodendrocyte lineage cell behavior contribute to our understanding of the biology of (re)myelination. Ultimately, this knowledge may lead to the identification of new therapeutic targets for disorders in which there is a failure of remyelination.

2. MMPs in the brain

The MMP-family can be grouped into interstitial collagenases, gelatinases, stromelysins, matrilysins, membrane-type-MMPs (MT-MMPs) and 'other MMPs' [31]. Table 1 provides an overview of relevant MMP substrates [31–34] and their effects on oligodendrocyte lineage cells. Virtually all MMPs are zinc-dependent enzymes that consist of three subunits (Fig. 1): (1) a prodomain, which includes a short peptide sequence at the N-terminal that labels the MMP for secretion, (2) a catalytic zinc-binding domain and (3) a hemopexin-like substrate-binding C-terminal domain (Fig. 1A). Variations on this basic structure affect substrate specificity, *e.g.* the addition of three fibronectin-like repeats enables MMP2 and -9 to degrade gelatins and collagens (Fig. 1B). MMPs are potent enzymes and therefore their activity needs to be tightly controlled. Except for the 6 membrane-type MMPs, which are anchored to the cell membrane as active enzymes [32] (Fig. 1C), most MMPs are secreted in the form of proMMPs. Cleavage of the prodomain, often by other MMPs, such as MMP3, leads to their activation [28]. In turn, tissue inhibitors of metalloproteinases (TIMPs) may act on the C-terminal domain in order to inhibit the enzymes in a 1:1 ratio [35]. Few MMPs, including MMP7, lack a C-terminal domain (Fig. 1D). These MMPs are particularly 'powerful', because, once active, they are more difficult to inhibit [36]. Recently, reversion-inducing cysteine-rich protein with kazal motif (RECK) has been proposed as a new inhibitor of MMP2, MMP9, MMP14 (MT1-MMP) and possibly MMP7 activity [37]. RECK is a membrane protein, which is found to be expressed in the CNS on NPCs in response to hypoxic-ischemic injury [38]. Although little is known about the contribution of RECK to MMP deactivation in the CNS during developmental myelination nor upon demyelinating injury, this discovery introduces an exciting new view on the interactions between MMPs and their inhibitors.

MMPs are found in practically every tissue, including the CNS. In healthy adult brain and spinal cord, levels of most MMPs are low or undetectable [35]. However, upon tissue remodeling, for example during revascularization or in response to injury, MMPs serve crucial functions in regulating the behavior of brain cells by cleaving receptors, growth factors and cytokines and degrading ECM proteins [39]. In the embryonic stage, ECM proteins act as important cues to guide cell behavior during the development of various organs, including the brain. For example, the ECM proteins collagen, hyaluronan and lumican are necessary for correct folding of the neocortex [40], while double knockout of laminin α2 and α4 in mice leads to radial glial cell apoptosis and decreased cortical size [41]. Accordingly, MMPs are highly expressed during CNS development and their activity is tightly regulated. Similarly, several MMPs, either endogenously expressed or extracellularly provided by adjacent glia or neurons, guide the behavior of oligodendrocyte lineage cells.

3. The role of MMPs in adult neural progenitor cell migration, proliferation and commitment to the oligodendrocyte lineage

3.1. From adult neural progenitor cell to oligodendrocyte progenitor cell

During early embryonic development, the outermost of the three primary germ layers, the ectoderm, gives rise to neuroepithelial precursor cells, which together form the neural plate. This sheet-like structure folds into a hollow cylinder called the neural tube, which will eventually become the brain and spinal cord. Shortly after formation of the neural tube, part of the neuroepithelial precursor cells differentiate into pluripotent radial stem cells (also called radial glia) [42]. They acquire an astrocyte-like morphology and start expressing glia-specific factors, such as vimentin and glial fibrillary acidic protein (GFAP) [43]. These radial stem cells reside in the primitive ventricular zones of the brain and spinal cord. First, they generate neural progenitors (brain) or motor neurons (spinal cord) and then, around the 6th week of gestation in humans, which corresponds to embryonic day 12–14 in rodents, switch to producing astrocytes and OPCs [42,44]. Distinct MMPs contribute to this process by influencing NPC migration, proliferation and differentiation (Fig. 2).

Table 1
Overview of (possible) functions of MMPs linked to oligodendrocyte lineage cells during developmental myelination, demyelination and efficient remyelination.

Subclass	MMP	CNS relevant substrates		(Possible) functions in oligodendrocyte lineage cells
		ECM proteins	Other proteins	
Interstitial collagenases	MMP1 (collagenase 1)	Collagen1 − 3, -7, -8, and -10, CSPGs (aggrecan, versican), perlecan, proteoglycan link protein, tenascin C.	IGFBP2 and -3 IL1β, MBP, PAR1, proTNFα, SDF1α.	Cleavage of PAR1 increases NPC proliferation and decreases oligodendrocyte lineage commitment. – Degrades MBP.
	MMP8 (collagenase 2)	Collagen-1-3, -5, -7, -8 and -10, CSPGs (aggrecan), laminin.	IL10, occludin.	*Unknown.*
	MMP13 (collagenase 3)	Collagen 1 − 5 and -9, − 11, CSPGs (aggrecan), fibronectin, hyaluronan, laminin, perlecan, tenascin C.	ProTGFβ, MBP, proTNFα, SDF1α.	Degrades MBP.
	MMP18 (collagenase 4)	Collagen.	*Unknown.*	*CNS expression unknown.*
Gelatinases	MMP2 (gelatinase A)	Collagen 1, -4, -5, -7, -10, -11 and -14, CSPGs, (aggrecan, brevican, neurocan, perlecan, versican), fibronectin, laminin, proteoglycan link protein, tenascin C, vitronectin.	Dystroglycan, galectin-3, IGFBP3, IL1β, integrin αvβ1, MAG, MBP, proIL1, SDF1α, TNFα.	Cleavage of SDF1α reduces NPC migration. – Degradation of integrin αvβ1 may facilitate OPC migration. – May aid OPC survival. – Possibly facilitates early oligodendrocyte differentiation by cleaving galectin-3. – Degrades MBP and MAG.
	MMP9 (gelatinase B)	Fibronectin, laminin, NG2, proteoglycan link protein, vitronectin.	Dystroglycan, galectin-3, IFNβ, IGFBP1 and -3, I, IL1β, IL2R, MAG, MBP, NCAM, proIL1β, proTNFα, proTNFβ, PSA-NCAM, SDF1α.	Promotes NPC migration and proliferation. – Influences OPC migration and survival by degrading fibronectin, laminin and vitronectin. – Facilitates oligodendrocyte process extension. – Degrades MBP and MAG. – May degrade myelination-inhibiting PSA-NCAM from axons.
Stromelysins	MMP3 (stromelysin 1)	Collagen-2, -4, -9 and -10, CSPGs (aggrecan, versican), fibronectin, laminin, proteoglycan link protein, tenascin C, vitronectin.	Citrullinated MBP, IGFBP1 and -3, IL1β, MBP, proIL1β, proMMP1, -7, -8, -9 and -13, SDF1α, TGFβ, TNFα.	Activates other MMPs. – Influences OPC migration and survival by degradation of fibronectin, laminin, vitronectin and tenascin C. – May influence OPC proliferation by cleaving IGFBP3, releasing IGF1. – Degrades MBP.
	MMP10 (stromelysin 2)	Collagen-2, -4 and -5, fibronectin, laminin.	*Unknown.*	Expressed by OPC and may influence OPC migration and survival by degrading fibronectin and laminin.
	MMP11 (stromelysin 3)	Laminin.	IGFBP1.	*Unknown.*
Matrilysins	MMP7 (matrilysin 1)	Collagen- 1- − 3, -5, -7, -8 and -10, CSPGs (aggrecan), fibronectin (aggregates), laminin, osteopontin, proteoglycan link protein, vitronectin.	MAG, MBP, N-cadherin, NMDAR, proTNFα.	Cleavage of N-cadherin may facilitate OPC migration, but reduce myelination by oligodendrocytes. – Cleavage of NMDAR may reduce myelination boligodendrocytes. – Degrades MBP and MAG. – May degrade remyelination-inhibiting fibronectin (aggregates).
	MMP26 (matrilysin 2)	Estrogen receptor β.	*Unknown.*	*Unknown.*
MT-MMPs	MMP14 (MT1-MMP)	Collagen 1 and − 3, CSPGs (aggrecan), DSPGs, fibronectin, laminin, lumican, NG2, perlecan, syndecan tenascin C, vitronectin.	ADAM9, integrin αvβ3, galectin-1, HSP90α, IL1β, IL8, proMMP2, and -13, SDF1α, TNFα.	Facilitates OPC migration on myelin, possibly by cleaving NG2.
	MMP15 (MT2-MMP)	Collagen 1 and − 3, CSPGs (aggrecan), fibronectin, laminin, perlecan, tenascin C, vitronectin.	ProMMP2.	*Unknown.*
	MMP16 (MT3-MMP)	Collagen-1 and -3, CSPGs (aggrecan), fibronectin, laminin, perlecan, vitronectin.	ProMMP2.	May facilitate NPC proliferation.
	MMP17(MT4-MMP)	ADAMTS4, fibronectin.	ProTNFα.	*Unknown.*
	MMP24 (MT5-MMP)	CSPGs, DSPGs, fibronectin, laminin.	ProMMP2, N-cadherin.	Increases NPC proliferation by cleaving N-cadherin.
	MMP25 (MT6-MMP)	Collagen 4, fibronectin.	Galectin1, golli-MBPs, IGFBP7, MBP, SPARC.	Degrades MBP.
Other MMPs	MMP12 (macrophage metalloelastase)	CSPGs (aggrecan), fibronectin, laminin, osteopontin, vitronectin.	IFNα, IFNγ, IGFBP6, MBP, proTNFα.	Ependymal cell-derived MMP12 decreases NPC proliferation *via* actions on ependymal cells and ECM. – Influences OPC migration and survival by degrading fibronectin, laminin and vitronectin. – Cleavage of IGFBP6 enhances oligodendrocyte differentiation. - Degrades MBP.
	MMP19	Fibronectin, CSPGs (aggrecan), laminin, tenascin C, vitronectin.	TNFα.	*Unknown.*
	MMP20	CSPGs (aggrecan).	*Unknown.*	*CNS expression unknown.*
	MMP21	*Unknown.*	*Unknown.*	*CNS expression unknown.*
	MMP23	Fibronectin.	*Unknown.*	*CNS expression unknown.*
	MMP27	*Unknown.*	*Unknown.*	*CNS expression unknown.*
	MMP28	*Unknown.*	NCAM, Nogo-A.	Cleavage of NCAM may increase OPC survival. – Cleavage of NCAM may decrease myelination by oligodendrocytes.

Substrates in bold are discussed in the text in the context of the according matrix metalloproteinase (MMP). Abbreviations: ADAM9 – a disintegrin and metalloprotease 9; ADAMTS4 - a disintegrin and metalloproteinase with thrombospondin motifs 4; CNS – central nervous system; CSPGs – chondroitin sulfate proteoglycans; DSPGs – dermatan sulfate proteoglycans; EC – ependymal cell; HSP90α – heat shock protein 90α; HTLV1 – human T-cell leukaemia virus type 1; IFN – interferon; IGFBP – insulin-like growth factor binding protein; IL – interleukin; MAG – myelin-associated glycoprotein; MBP – myelin basic protein; NCAM – neural cell adhesion molecule; NG2 – neuron-glial antigen 2; NMDAR – *N*-methyl-D-aspartate receptor; NPC – neural progenitor cell; OPC – oligodendrocyte progenitor cell; PAR1 – protease-activated receptor 1; PSA-NCAM – polysialylated NCAM; SDF1α – stromal cell-derived factor 1α; TGFβ – transforming growth factor β; TNFα – tumor necrosis factor α.

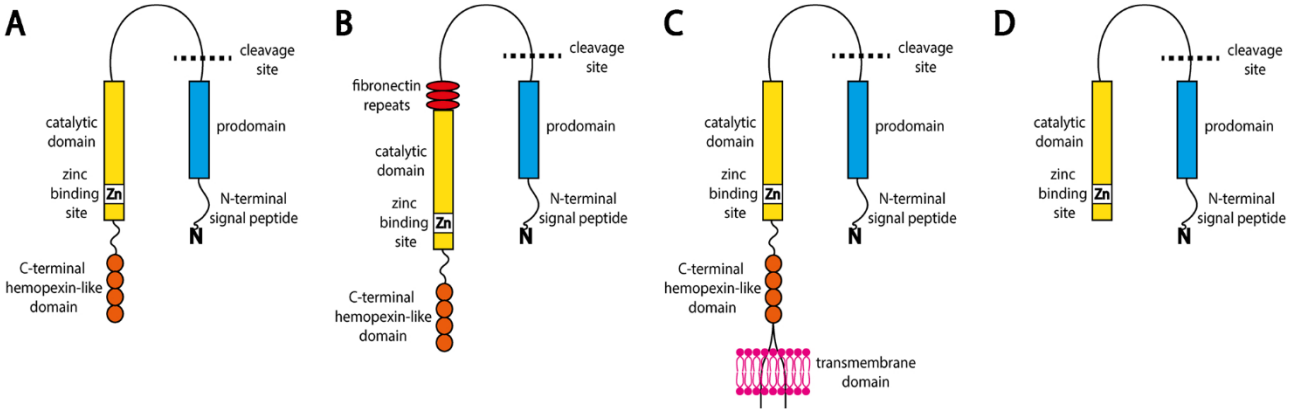

Fig. 1. Schematic overview of the structure of MMPs. A. Basic matrix metalloproteinase (MMP) structure. **B**. MMP containing fibronectin-like repeats (MMP2 and -9). **C**. Simplified representation of a membrane-type MMP. **D.** Structure of a minimal domain MMP (MMP7 and -26).

3.2. MMPs influence migration patterns of neural progenitor cells

In most organs, the ECM mainly exists in the form of the basal lamina, *i.e.*, a thin yet dense layer of ECM proteins that delineates individual cells or groups of cells, *e.g.*, muscle fibers. However, in the CNS the architecture of the ECM is profoundly different. Compared to other tissues, the adult brain is relatively devoid of 'classical' fibrous ECM glycoproteins like collagen, fibronectin and vitronectin and enriched in hyaluronan [45,46]. Neurons and glia are not surrounded by well-defined basal laminas, but by a loose network of ECM proteins, which mostly consists of proteoglycans [15]. Higher density of ECM proteins is only found in the basal lamina of blood vessels, perineuronal nets and in specialized stem cell niches of the brain, such as the subventricular zone [15]. Contrastingly, classical ECM proteins are highly expressed during CNS development in order to provide newborn cells with the appropriate cues for migration, proliferation and differentiation. Not surprisingly, this necessitates the presence of MMPs. MMP2, -3, -7, -9, -11, -12, -13, -14, -15 and -24 mRNA are detected in the developing mouse brain directly after birth and transcripts of MMP2, -9, -11, -13, -14, -15 and -24 are significantly upregulated one week postnatally compared to later time points [47,48]. Expression of some of these MMPs differs between CNS regions, *e.g.*, MMP9 mRNA levels are elevated in the spinal cord, optic nerve and corpus callosum, while MMP24 mRNA levels are more highly expressed in the hindbrain [47].

MMP2, endogenously expressed by NPCs [49], inhibits NPC migration by cleaving the chemokine stromal cell-derived factor 1α (SDF1α) (Fig. 2A-1, A-2). SDF1α is expressed by astrocytes and NPCs and is abundantly present in the developing nervous system [50], where it can bind to the chemokine receptor type 4 (CXCR4) on NPCs [50,51]. CXCR4 receptor activation by SDF1α increases intracellular calcium levels in NPCs through downstream signaling involving cyclic AMP. In response to SDF1α-mediated CXCR4 receptor activation, human fetus-derived NPCs successfully migrate in specialized chemotaxis chambers [51]. MMP2, and possibly MMP1, -3, -9, -13 and -14 [52], cleaves a small four amino acid sequence of the N terminal of SDF1α, yielding 'SDF1(5-67)', which is unable to bind to CXCR4 and stimulate NPC migration. Thus, in the developing brain, MMP2 decreases NPC migration by cleaving SDF1α. Contrastingly, earlier studies found that stimulation of NPCs with the pro-inflammatory cytokines TNFα or IFNγ, simultaneously increased secretion of active MMP2 and proMMP9 [53] and enhanced NPC migration [54]. Possibly, the negative effect of MMP2 on migration is outweighed by a positive effect of MMP9, as selective inhibition of MMP9 reduces NPC migration (and proliferation) in response to hypoxia [55] (Fig. 2A-3). Alternatively, the pro-inflammatory cytokine stimulation may alter expression levels of other proteases. For example, MMP1 also cleaves SDF1α [52] and MMP1 mRNA is observed in migrating rabbit fetal brain cells after their transplantation into mouse brain [56] (Fig. 2A-4).

3.3. MMPs affect neural progenitor cell proliferation and differentiation

In addition to playing a role in migration, MMPs have been

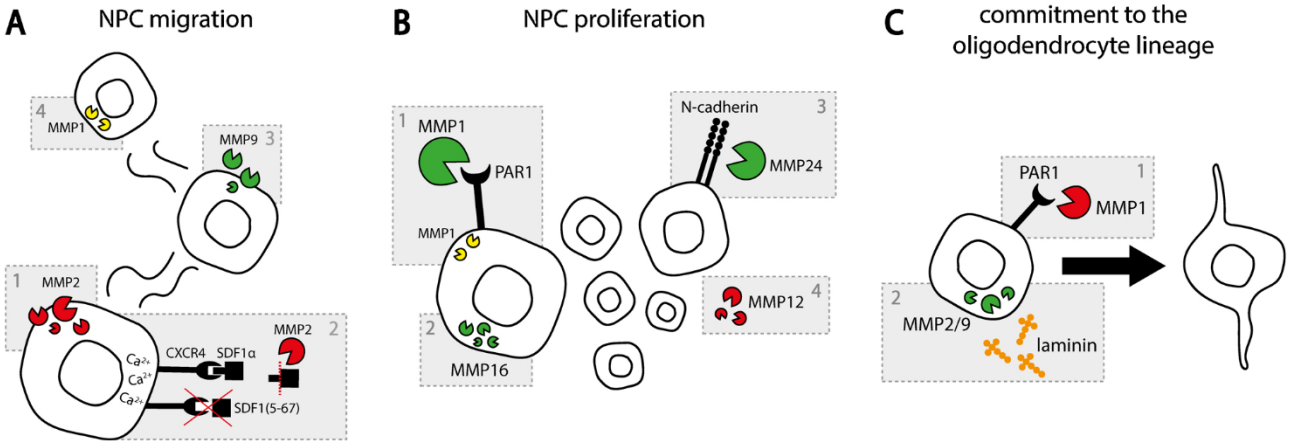

Fig. 2. The role of MMPs in adultneural progenitor cellmigration, proliferation and commitment to the oligodendrocyte lineage. A. Neural progenitor cell (NPC) migration. **B**. NPC proliferation. **C**. commitment to the oligodendrocyte lineage. Matrix metalloproteinases (MMPs) are depicted in green when they have a positive effect on the behavior of the cell in question, in red for a negative effect and in yellow if the effect is yet unknown. CXCR4 - chemokine receptor type 4; PAR1 - protease-activated receptor 1; SDF1α - stromal cell-derived factor 1α. See text for details.

implicated in NPC proliferation. Similar to other proteases including thrombin and kallikrein 6, MMP1 cleaves and activates protease-activated receptor 1 (PAR1) [57]. PAR1-4 are a family of G-protein coupled receptors expressed on neuronal and glial cells that are involved in NPC proliferation and differentiation [58]. As aforementioned, MMP1 is observed in transplanted neuroprogenitor cells in the rodent brain [56]. Moreover, *in vitro* human-derived astrocytes [59] and monocytes [60] exhibit increased secretion of MMP1 in response to pro-inflammatory cytokines. MMP1-mediated PAR1 activation increases NPC proliferation, but decreases the differentiation of NPCs into OPCs [57,58] (Fig. 2B1, C1). Compared to wildtype, NPCs isolated from mice that are genetically engineered to overexpress human MMP1 in neuroprogenitor (derived) cells under the control of a GFAP promotor, exhibit enhanced proliferation *in vitro* and *in vivo* [57]. In culture, this effect could be reversed by addition of a broad-range MMP inhibitor or by adding PAR1 inhibitors [57]. In comparison to wildtype mice, cultures from human MMP1 overexpressing mice show a decrease in OPC numbers and an increase in the number of neurons [57]. In line with this, adult PAR1$^{-/-}$ mice demonstrate the exact opposite, namely increased numbers of oligodendrocytes in the corpus callosum and anterior commissure [58]. Thus, PAR1 activation by MMP1 likely influences developmental myelination by increasing NPC proliferation, but decreasing oligodendrocyte lineage commitment (Fig. 2B-1, C-1).

Another MMP that may play a role in NPC proliferation is MMP16 or MT3-MMP (Fig. 2B-2). MMP16 is abundantly present in the medium of human fetus-derived neural progenitors, but its levels decrease when the NPCs are transfected with Olig2, a transcription factor that is crucial for oligodendrocyte development [61]. Culturing NPCs in the presence of methylprednisolone, an anti-inflammatory drug with impaired neurogenesis as a known side effect [62], reduces MMP16 protein expression and decreases NPC proliferation, but increases myelin membrane formation by the OPC progeny [63]. Similarly, culturing NPCs on laminin, an ECM protein that is known to stimulate myelination [19,64,65], led to an increase in gelatinase (MMP2 and/or -9) expression and a higher percentage of oligodendrocyte offspring [66] (Fig. 2C-2).

Finally, MMPs may also influence NPC behavior by affecting the interaction between NPCs and their surrounding cells. For example, in the subventricular zones of the brain MMP24 (MT5-MMP) is expressed by NPCs and ependymal cells [67]. Here, MMP24 promotes NPC proliferation by cleaving N-cadherins (Fig. 2B3), which are adhesion proteins that enable contact between NPCs and ependymal cells [67]. Ependymal cells are found in close contact with NPCs in the subventricular zones of the adult brain, where they are arranged around NPCs in pinwheel-like formations [68]. In addition to secreting cerebrospinal fluid, these ependymal cells influence NPC behavior by providing trophic support and producing ECM proteins [69]. During differentiation *in vitro*, ependymal cells upregulate their mRNA and protein levels of MMP12, but not other MMPs [70]. Blocking of MMP activity with the broad-spectrum MMP inhibitor GM6001 reduces ependymal cell differentiation. Moreover, loss of extracellular MMP12 *in vivo* changes ependymal cell organization, ECM deposition and increases the number of NPCs, indicating that ependymal cell-derived MMP12 inhibits NPC proliferation [70] (Fig. 2B-4).

4. The role of MMPs in oligodendrocyte progenitor cell recruitment and survival

4.1. Oligodendrocyte progenitor cells in central nervous system development

Radial stem cells produce three consecutive waves of OPCs from different regions of the ventricular zone. OPCs are defined by their expression of the membrane proteoglycan neuraon-glial antigen 2 (NG2), platelet derived growth factor receptor α (PDGFRα) and the transcription factors Olig1, Olig2 and Sox10 [43]. Around birth, the first wave of ventrally-derived OPCs starts disappearing from the brain, while the more dorsally-derived second (≈20 %) and especially the third wave (≈80 %), the latter originating from the cortical ventricular zones, continue to migrate until OPCs are present throughout the entire brain [71]. Contrastingly in the spinal cord, the first wave of ventrally-derived OPCs remains present in the ventral part of the spinal cord and is only replaced by the second wave of dorsal OPCs in the dorsal spinal cord [42,43]. The movements of OPCs arerguided by cues from the microenvironment, such as increasing concentration gradients of signaling molecules (*e.g.*, semaphorins, bone morphogenic protein and sonic hedgehog), growth factors (*e.g.*, PDGF and fibroblast growth factor) and ECM proteins (*e.g.*, laminin, fibronectin and vitronectin) [72]. Neuronal activity and brain vasculature also play an important role in OPC migration; to make sure the OPC will not only choose the right axon to myelinate, but also has access to adequate oxygen and nutrient supply to complete this energy-consuming task (reviewed by [73]).

Many signals, including PDGF and fibronectin, that are known to stimulate OPC migration, also increase OPC proliferation. However, at a certain point, the sum of factors from the OPC's niche will shift and become more inhibitory for migration and more permissive for proliferation. Then, the migrating OPC will halt and start proliferating until a homeostatic balance in OPC numbers is reached. At the end of developmental myelination, the proportion of OPCs hoovers around 5–8 % of total brain cells, which will be maintained into adulthood [5]. During developmental myelination, several MMPs influence the recruitment and survival of OPCs by degrading ECM proteins, which also releases growth factors, as well as by direct cleaving of cell surface receptors and growth factors (Fig. 3).

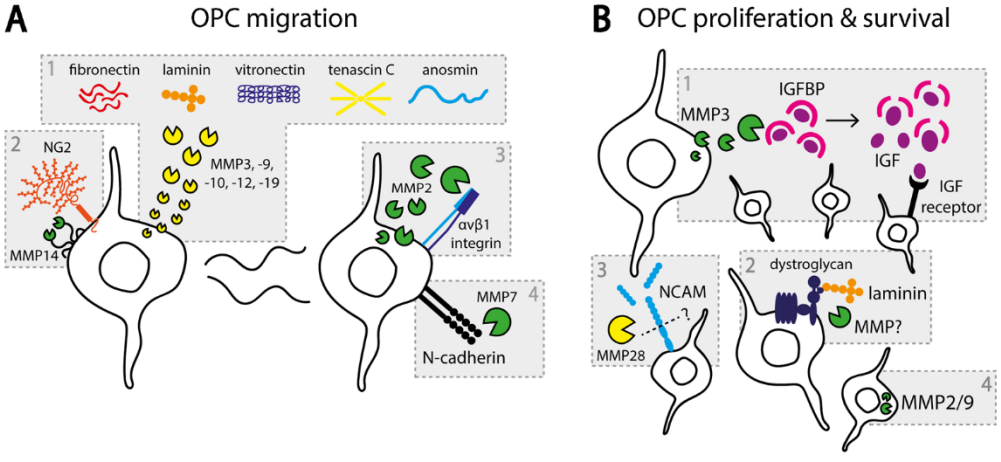

Fig. 3. The role of MMPs inoligodendrocyte progenitor cellmigration, proliferation and survival. A. Oligodendrocyte progenitor cell (OPC) migration. **B.** OPC proliferation and survival. Matrix metalloproteinases (MMPs) are depicted in green when they have a positive effect on the behavior of the cell in question, in red for a negative effect and in yellow if the effect is yet unknown. If the effect on a substrate is known, but the protease in question has not yet been identified, this is written as 'MMP?'. IGF - insulin-like growth factor; IGFBP - IGF-binding protein; NCAM - neural cell adhesion molecule; NG2 - neuron-glial antigen 2. See text for details.

4.2. MMPs facilitate oligodendrocyte progenitor cell migration

On their journey through the developing brain, OPCs employ proteases to make their way through the ECM and along axonal tracts or blood vessels. *Olig2*-transfected human fetus-derived NPCs exhibit increased secretion of MMP3, -9, -10, -12 and -19 [61]. These MMPs cleave a number of ECM proteins known to influence OPC migration, including fibronectin (MMP3, -9, -10, -12, -19), laminin (MMP3, -9, -10, -12, -19), vitronectin (MMP3, -9, -12, -19), tenascin-C (MMP3, -19) and possibly anosmin [74] (Fig. 3A-1, Table 1). An early investigation using CG4 cells, a cell line generated from primary rat OPCs, showed that a metalloproteinase, later identified to likely be MMP14/MT1-MMP [75], possibly facilitates migration of OPCs along myelin tracts in the CNS, particularly in the white matter [76]. *In vitro*, OPCs can differentiate into astrocytes as well as oligodendrocytes [77,78]. CG4 cells that are allowed to differentiate into astrocytes are unable to migrate on purified myelin. Contrastingly, OPCs initiate attachment and process extension equally well on myelin-coated compared to uncoated membranes as well as on decellularized spinal cord sections [76]. Experiments with primary rat-derived OPCs show similar results [76]. Intriguingly, a later study showed that MMP14 is likely responsible for cleaving a small part of the membrane-spanning CSPG NG2 from the surface of OPCs [79]. This process leaves a truncated form of NG2 on the cell membrane [79], which may influence OPC migration as interactions of NG2 with a number of proteins initiate cytoskeletal changes that change the cell's polarity, moving the OPC forwards [80]. In a different manner, MMP2, of which mRNA levels are increased in the developing brain one week after birth [47], may also promote OPC migration. Invasive colon cancer cells have high expression of MMP2, which they use to degrade integrin αvβ1, enhancing their motility and invasiveness [81]. Integrins are the connecting proteins between cells and the ECM and are well-known to regulate OPC migration, proliferation, differentiation [20,82,83] and survival [64,84]. *In vitro*, integrin αvβ1 is expressed on rat OPCs [18,85], where it facilitates migration [18]. Cultured murine OPCs secrete (active) MMP2 [86,87], although possibly to a lesser degree than NPCs [49], making it tempting to speculate that in analogy to cancer colon cells, MMP2-mediated degradation of integrin αvβ1 iaids OPC migration in the developing brain (Fig. 3A-3).

In addition to degrading ECM proteins, MMPs cleave cell surface proteins and growth factors that can influence the migration patterns of OPCs. For instance, MMP7 cleaves the ectodomain of recombinant and cell-associated N-cadherin [88]. N-cadherin is a transmembrane protein that mediates cell to cell adhesion by binding to cadherins and other membrane proteins on surrounding cells. This adhesion protein is expressed on oligodendrocyte lineage cells, astrocytes and neurons [89,90]. The presence of N-cadherin on astrocytes enhances astrocyte-oligodendrocyte adhesion and reduces the migration of oligodendrocytes on an astrocyte monolayer [90]. Moreover, N-cadherin facilitates developmental myelination by strengthening the interaction between oligodendrocyte processes and neuronal axons [91,92]. Following this reasoning, cleavage of N-cadherin by MMP7 may increase OPC migration, while inhibiting myelination by mature oligodendrocytes (Fig. 3A-4).

4.3. MMPs regulate oligodendrocyte progenitor cell proliferation

Besides OPC migration, a number of MMPs may also influence OPC proliferation. For example, insulin-like growth factors (IGFs), *e.g.*, IGF1, bind to IGF receptors on OPCs, stimulating their proliferation [93]. Normally, virtually all IGFs are bound by IGF-binding proteins (IGFBPs), rendering them unavailable to exert their biological activity [94]. However, cleavage of the IGF-IGFBP3 complex by MMP3, and likely other MMPs including MMP1, -2, and -9 [95,96], frees IGF1, allowing its binding to IGF receptors to stimulate cell proliferation [96] (Fig. 3B-1). Secretion of these MMPs by other glial cells in the developing brain may increase OPC proliferation by regulating the bioavailability of IGF. Finally, the membrane receptor dystroglycan is expressed on oligodendrocyte lineage cells and its extracellular portion binds to laminins [65], connecting the cell to the ECM. On OPCs, but not oligodendrocytes, the selective cleavage of laminin-211-bound dystroglycan by a yet unidentified endogenous metalloproteinase stimulates OPC proliferation (Fig. 3-B2). Although dystroglycan cleavage could be inhibited by MMP inhibitors and MMP2 and -9 are known to cleave dystroglycan, neither of these MMPs was found to be responsible for cleaving dystroglycan on OPCs [97].

4.4. MMPs may regulate oligodendrocyte progenitor cell survival

Not all OPCs will survive to ultimately become myelinating oligodendrocytes. In initial brain development, a large surplus of OPCs is produced in comparison to the number of axons [98]. However, the availability of survival signals, such as PDGF and axonal contact, is limited and depending on the brain region up to 50 % of premyelinating OPCs will go into apoptosis [98,99]. In postnatal brain development, MMP-mediated release, activation and/or degradation of survival signals plays a role in regulating OPC life or death. For instance, a number of MMP substrates have been shown to enhance OPC survival, including growth factors, such as IGF1 [100], and ECM proteins, like laminin [101]. NCAM is a transmembrane glycoprotein that is expressed on the

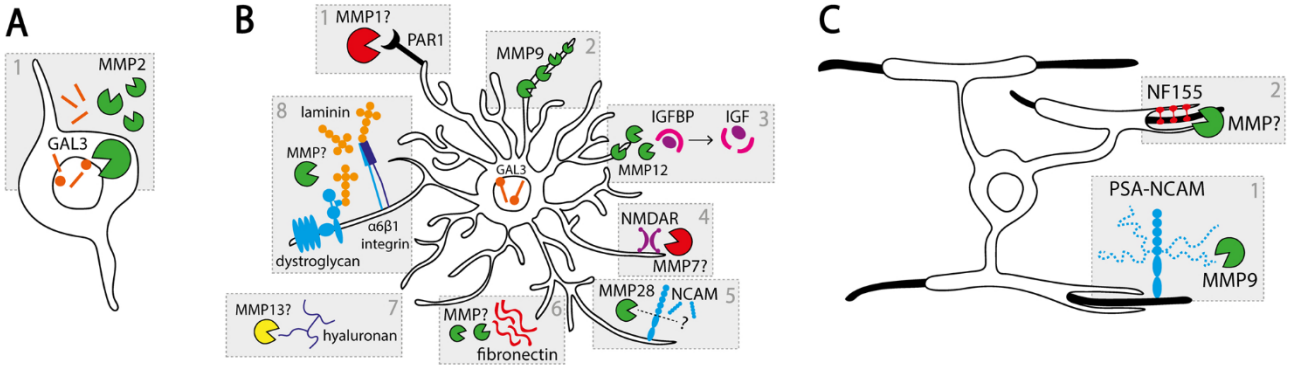

Fig. 4. The role of MMPs in oligodendrocyte process extension and developmental myelination. A. Oligodendrocyte progenitor cell. **B**. Premyelinating oligodendrocyte. **C**. Mature oligodendrocyte. Matrix metalloproteinases (MMPs) are depicted in green when they have a positive effect on the behavior of the cell in question and in red for a negative effect. If the effect on a substrate is known, but the protease in question has not yet been identified, this is written as 'MMP?'. When the effect of an MMP on a substrate is known, but this effect has not been directly demonstrated in the context of the oligodendrocyte lineage, a question mark is added, *e.g.*, 'MMP1?'. GAL3 - galectin-3; IGF - insulin-like growth factor; IGFBP - IGF-binding protein; NCAM - neural cell adhesion molecule; NF155 - 155 kDa neurofascin; NMDAR - *N*-methyl-D-aspartate receptor; PAR1 - protease-activated receptor 1; PSA-NCAM - polysialylated-NCAM. See text for details.

surface of neuronal axons and oligodendrocytes. *In vitro*, NCAM, or more specifically a short amino acid sequence within the NCAM protein, called the FRM region, increases survival of premyelinating oligodendrocytes [102]. MMP28, which is expressed on neuronal axons [103,104], and maybe OPC-derived MMP9 [105], cleaves NCAM, possibly influencing the effect of NCAM on OPC survival (Fig. 3B-3). Lastly, in fetal ovine mixed glia cultures, inhibition of MMP2 and MMP9 activity by the gelatinase inhibitor SB-3CT further decreased long term OPC survival following LPS treatment, possibly indicating that MMP2 and/or MMP9 are beneficial to OPC survival [106] (Fig. 3B-4).

5. The role of MMPs in oligodendrocyte process extension and developmental myelination

5.1. From oligodendrocyte progenitor cell to myelinating oligodendrocyte

At birth, the human brain is virtually devoid of myelin. Developmental myelination is quickly initiated and will be mostly completed in the first year after birth, although in some brain areas, *e.g.*, the cortex, myelin production will continue well into puberty [107]. Similarly, in rodents developmental myelination starts directly after birth and is almost complete around postnatal day 60 [107]. For proper brain myelination, OPCs need to differentiate into mature myelinating oligodendrocytes. This is a complex process that is mediated by a plethora of promoting and inhibitory factors from the cell's microenvironment. As the OPC differentiates, it will downregulate NG2 and PDGFRα expression and start expressing mature oligodendrocyte markers, such as myelin oligodendrocyte protein (MOG), myelin basic protein (MBP), proteolipid protein (PLP) and cyclic nucleotide 3'-phosphohydrolase (CNP). *In vivo*, one oligodendrocyte can myelinate up to 80 axon segments [107]. The maturing oligodendrocyte extends and retracts its processes in search for nearby permissive axons and, upon receiving the right extracellular cues, will enwrap short segments of neuronal axons in a multi-layered myelin sheath [108]. Unmyelinated segments, called the nodes of Ranvier, are present at regular intervals along the axon and enable fast saltatory conduction. The nodes of Ranvier are characterized by a high density of sodium channels and cytoskeletal proteins and are surrounded by a specialized ECM [109]. The individual layers of the myelin sheath are about 12 nm thick and consist of a double lipid bilayer (predominantly made up of cholesterol, phospholipids, galactolipids and plasmalogens) interspersed with myelin proteins (including MBP, PLP, MOG, MAG, CNP and claudin 11) [108]. The inner- and outermost loops of the myelin sheath, respectively termed the adaxonal and abaxonal layer, are made up of non-compact myelin, which is enriched in myelin proteins like MOG (only the abaxonal layer), MAG (only the adaxonal layer) and CNP. The remaining layers consists of tightly stacked compact myelin and have high content of PLP and MBP [110]. Non-compact myelin is also found at the paranodes, which are the ends of the myelin segments that surround the nodes of Ranvier. Here, there are specialized adhesion proteins present, such as oligodendroglial neurofascin 155 (NF155), that enable a tight interaction between axon and myelin sheath. Moreover, non-compact myelin is present in cytoplasmic channels in the myelin sheath, which allow communication of the axon with the outside world, *e.g.*, by the transfer of nutrients [108,110]. During developmental myelination, oligodendroglia-derived MMP9 and MMP12 are involved in the morphological differentiation of oligodendrocytes [48,111–113], while other extracellular MMPs aid to generate a myelination-permissive environment by removing inhibitory cues for OPC differentiation (Fig. 4).

5.2. Loss of MMPs alters, but does not prevent, myelin formation

In the mouse brain and spinal cord, mRNA levels of MMP2, -9, -11, -13, -14, -15 and -24 are increased 1 week after birth, implying a role for these MMPs in brain and/or myelin development [47,48]. Nevertheless, the few studies that have investigated the effects of experimental knockout of individual MMPs on the mouse brain do not show gross deficiencies in myelin formation [114], implying a certain redundancy of (individual) MMPs in the context of developmental myelination. Although the impact of MMP1 knockout on myelin formation has not been investigated, transgenic overexpression of MMP1 influences the differentiation of NPCs into OPCs through MMP1-mediated PAR1 activation [57] (Fig. 2B1&C1). In addition, cleavage of PAR1 by MMP1 may influence myelinating efficiency of oligodendrocytes. Adult PAR1-/- mice have more oligodendrocytes, thicker myelin sheaths and show increased PLP and MBP expression [115]. PAR1 is abundantly expressed on oligodendrocyte lineage cells [116,117] and its cleavage leads to impeded oligodendrocyte process outgrowth and myelin membrane formation *in vitro* [117]. Thus, during brain development, MMP1-mediated PAR1 cleavage may play a role in regulating myelination by controlling oligodendrocyte numbers and/or myelin production (Fig. 4B-1).

In contrast to MMP1, oligodendroglia-derived MMP9 promotes morphological differentiation of oligodendrocytes (Fig. 4B-2). MMP9 mRNA is transiently expressed in the developing mouse optic nerve and corpus callosum [48,111,112] and *in vitro* gelatinase activity (MMP2 and/or 9) is found in rat OPCs and oligodendrocytes as well as in OPCs derived from a human NPC line [49]. In cultured human oligodendrocytes, MMP9 activity gradually increases in response to phorbol esters, which induce process extension, while MMP2 activity decreases [111]. Moreover, loss of MMP9 leads to impaired oligodendrocyte process extension *in vitro* [112] and developmental myelination *in vivo* [48]. Here, MMP9 is expressed at the tips of oligodendrocyte processes, where it facilitates process extension [112] (Fig. 4B-2). Although mRNA levels of most MMPs quickly decline after birth, MMP12 mRNA expression gradually increases during postnatal brain development [47,48]. *In vitro*, oligodendrocytes highly express MMP12 mRNA and MMP12 transcription is upregulated during process extension [113]. Loss of MMP12 reduces the morphological maturation of oligodendrocytes, while exogenous application of MMP12 almost completely rescues this phenotype. Moreover, in MMP12$^{-/-}$ mice the numbers of mature oligodendrocytes are reduced and myelination is delayed [48]. Interestingly, exogenous administration of IGF1 rescues the maturation of MMP12-deficient oligodendrocytes *in vitro*. As MMP12, similar to MMP3 and MMP9 [118], is able to cleave IGFBPs, including IGFBP6, MMP12 expression may contribute to oligodendrocyte maturation and myelination by increasing the bioavailability of IGF [48] (Fig. 4B-3). Of note, double knockout of MMP9 and MMP12 does not exacerbate the transient delay in myelination seen with knockout of only one MMP [48]. This either means that MMP9 and MMP12 have overlapping functions during developmental myelination and/or that a third MMP (or other protease) compensates for their absence, illustrating the large redundancy of MMPs with regards to substrate specificity.

5.3. MMPs regulate myelination by cleaving (membrane) proteins

MMP2 cleaves galectin-3, which is a β-galactoside-binding lectin of approximately 30 kDa that associates with receptors on oligodendrocyte lineage cells, astrocytes and microglia [86]. Galectin-3 is a positive regulator of myelination [86]. *In vitro*, recombinant galectin-3 increases oligodendrocyte differentiation, while conditioned medium from wildtype, but not galectin-3$^{-/-}$ microglia, similarly promotes oligodendrocyte maturation [86]. *In vivo*, galectin-3$^{-/-}$ mice exhibit fewer demyelinated axons and thinner myelin sheaths in the corpus callosum. Intriguingly, both (active) MMP2 and a 17 kDa cleavage product of galectin-3 are present in the medium of OPCs (Fig. 4A-1), but not of mature oligodendrocytes [86] (Fig. 4B). In breast cancer cells, cleavage by gelatinases is required for secretion of galectin-3 [119]. Here, the interaction between MMP2 and galectin-3 may take place at the cell membrane or even intracellularly [119]. Mature oligodendrocytes do not express MMP2 [49,86] and have higher levels of

galectin-3, corresponding to a lack of MMP2-mediated galectin-3 cleavage [86]. This points to a possible role for MMP2-mediated galectin-3 cleavage during early oligodendrocyte differentiation [86] (Fig. 4A-1, 4B).

Another MMP substrate that influences developmental myelination is the *N*-methyl-D-aspartate receptor (NMDA) receptor. NMDA receptors are voltage-gated calcium channels that are mainly expressed on neurons, but also on oligodendrocytes [120], where their activation leads to enhanced glucose uptake by promoting membrane localization of glucose transporter 1 [121]. Interestingly, the NMDA receptor can be cleaved by MMP7 [36] (Fig. 4B-4). Treatment of acute cortical slices with recombinant MMP7 leads to cleavage of the NR1 and NR2 subunits of the NMDA receptor resulting in reduced calcium influx in pyramidal neurons [36]. Although the effect of MMP7 on NMDA receptor function in oligodendrocytes was not examined, MMP7 may also cleave NMDA receptors on oligodendrocytes, possibly altering glucose metabolism, which could (negatively) influence developmental myelination (Fig. 4B-4).

In the CNS of mice and frogs, neurons express MMP28 during embryonic development [103]. Incubation of recombinant MMP28 from *Xenopus*, *i.e.*, the African clawed frog, with embryonic rat brains leads to degradation of NCAM and Nogo-A, both associated with myelin membranes [103]. In primary rat OPCs, NCAM is present at low levels and increases during maturation into (pre)myelinating oligodendrocytes [102]. Interestingly, binding of the extracellular domain of NCAM to the fibroblast growth factor receptor on oligodendrocyte lineage cells leads to increased survival, but not increased proliferation, of premyelinating oligodendrocytes *in vitro* [102]. Moreover, contact of OPCs with the cell-bound, but not the soluble form of NCAM accelerates oligodendrocyte process formation [102]. Thus, cleavage of NCAM by neuron-derived MMP28 may play a role in regulating oligodendrocyte survival and differentiation (Fig. 4B-5). In addition, MMP9 has recently been implicated in cleavage of polysialylated NCAM (PSA-NCAM) [122]. NCAM polysialylation, *i.e.*, the addition of α-2,8- polysiliac acid chains to the extracellular domain of NCAM, inhibits NCAM-NCAM interactions, reducing cell adhesion [123]. PSA-NCAM is expressed on neuronal axons during early brain development and its removal, for which MMP9 may be a candidate, is required for oligodendrocytes to contact the axon and initiate myelination [124] (Fig. 4C-1).

Lastly, cleaving of the extracellular domain of oligodendrocyte-specific NF155 by an unidentified metalloproteinase is important for its proper transport in oligodendrocyte processes. As NF155 is a cell adhesion molecule that enables a tight interaction between the paranodal loops and the axonal membrane, processing of NF155 by metalloproteinases may regulate the formation of paranodal junctions [125] (Fig. 4C-2).

5.4. MMPs degrade extracellular matrix proteins that inhibit oligodendrocyte differentiation

Naturally, the most notorious function of MMPs is remodeling of the extracellular landscape in the oligodendrocyte niche through degradation of ECM proteins. During brain development, several ECM molecules are expressed that promote the migration, proliferation and survival of OPCs. However, to allow proper differentiation of OPCs into myelinating oligodendrocytes, it is crucial that some of these proteins disappear in a timely fashion, implicating an important role for MMPs. For example, fibronectin is highly expressed in the developing brain, where it positively influences OPC proliferation, and possibly migration, *via* the EIIIA domain on astrocyte-derived fibronectin [18,22,101]. Nevertheless, fibronectin negatively affects OPC differentiation by dysregulating MMP9 activity, thereby inhibiting the formation of branched processes [126]. Therefore, timely removal of fibronectin may be necessary for the initiation of developmental myelination. Many MMPs, including MMP3, -7, -12 and -13, of which mRNA levels are detected in the developing brain [47,48], have been implicated in fibronectin degradation (Fig. 4B-6). Similarly, the ECM protein hyaluronan is most highly expressed in the neonatal brain and declines in the first two weeks after birth [127]. The high molecular weight form of hyaluronan is secreted by cultured astrocytes [128]. Degradation of hyaluronan by OPCs yields a low molecular weight form of hyaluronan that decreases proliferation and maturation of rat OPCs *in vitro* [128–131]. Although hyaluronan turnover is mainly orchestrated by a specific group of enzymes called hyaluronidases [132], MMP13, which can be secreted by astrocytes [133], may also play a role in hyaluronan degradation [134] (Fig. 4B-7). Moreover, presence of hyaluronic acid increases expression levels of a number of MMPs in keratocytes and fibroblasts, including MMP2 and -9 [135], while inhibition of hyaluronidases decreases MMP7 expression and activity in a cancer cell line [136]. Thus, degradation of myelination-inhibiting ECM proteins by MMPs may be a prerequisite for successful myelination. On the other hand, (over)expression of MMPs in the developing CNS may lead to the degradation of ECM proteins that positively influence OPC differentiation and myelination. Laminin, which is expressed in the developing brain [137], can be degraded by a number of MMPs, and binding of laminin to its receptors α6β1 integrin and dystroglycan on oligodendrocyte lineage cells promotes survival and myelin membrane formation [19,65,138,139] (Fig. 4B-8). Most likely, healthy developmental myelination is enabled by a tight balance between local production of ECM proteins and their timely clearance by MMPs. More research into the spatial and temporal distribution of ECM proteins and MMPs during development is necessary to further elucidate this complex process.

6. The role of MMPs in toxicity to oligodendrocytes, myelin degeneration and the (onset of) demyelination

6.1. Demyelination in health and disease

During life, damage to the myelin sheath may occur in the context of neurological conditions such as stroke, small vessel disease, traumatic brain injury, Krabbe's disease or MS [140,141]. Demyelination results in the loss of fast saltatory impulse conduction and leaves axons bare and vulnerable to degeneration. The resulting decreased nerve signal velocity and secondary neurodegeneration can give rise to a myriad of sensory, motoric and cognitive symptoms, depending on the brain area affected [140]. In acquired myelin disorders, such as MS, the demyelinating injuries occur focally and initially in a relapsing-remitting pattern, resulting in *e.g.*, (temporary) loss of vision, walking difficulties, bladder dysfunction or fatigue [142,143]. While in genetic disorders, *e.g.*, Krabbe's disease, demyelination is more progressive and diffuse, leading to severe seizures, complete loss of muscle tone and eventually death [141]. Virtually all demyelinating disorders are characterized by (secondary) activation of microglia and astrocytes, BBB leakage, recruitment of inflammatory cells from outside the CNS and eventually scar formation [142]. Theoretically, demyelination can either be due to toxicity to oligodendrocytes, resulting in a failure of oligodendrocytes to maintain the myelin sheath, *e.g.*, in response to inadequate nutrient supply during hypoxic ischemic injury, or by direct damage to the myelin sheath itself, *e.g.*, as a result of mechanical trauma or due to an attack by autoreactive T cells, as has long been hypothesized to be the etiology of MS [144]. It is difficult to establish the chicken and the egg, as both events may occur simultaneously and as damage to one component of the oligodendrocyte-myelin unit will quickly compromise the other. In both scenarios, MMPs play a role in demyelination through their ability to degrade myelin proteins and through their (indirect) actions on oligodendrocytes (Fig. 5).

6.2. MMPs degrade myelin proteins

MOG and MAG are both transmembrane proteins that extend through the myelin sheath, making these proteins 'visible' to

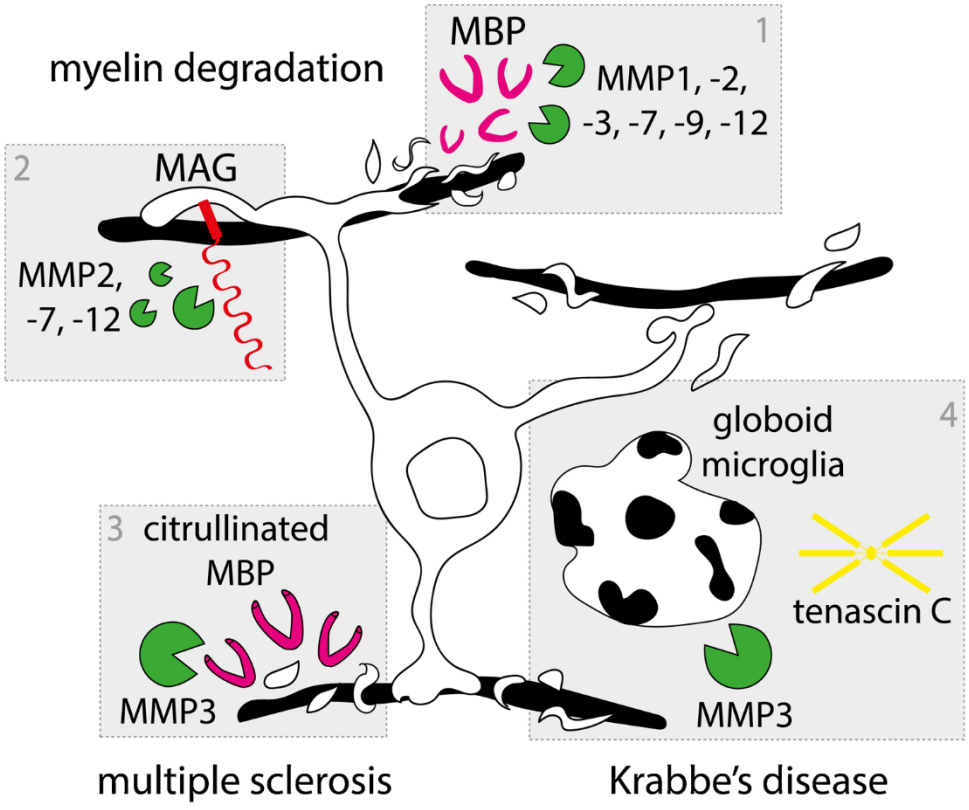

Fig. 5. The role of MMPs in toxicity to oligodendrocytes, myelin degeneration and (the onset of) demyelination. Matrix metalloproteinases (MMPs) are depicted in green when they have a positive effect on the behavior of the cell in question. MAG - myelin-associated glycoprotein; MBP - myelin basic protein. See text for details.

surrounding cells and more susceptible to (MMP-mediated) cleavage, when the myelin sheath is still intact [108]. However, while MOG may be readily accessible to MMPs, MAG may only be available for MMPs when myelin slightly detaches from the axon [145]. Contrastingly, MBP and PLP are 'hidden' within compact myelin [110], making these proteins unavailable for degradation by extracellular MMPs, unless damage to the myelin sheath has already occurred. In the demyelination phase of the experimental cuprizone model, mRNA expression of MMP3, -9, -12 and -14 is increased in the cortex and/or corpus callosum, while MMP15 and MMP24 mRNA levels are decreased [146]. Early reports already showed that (recombinant) human MMP1, -3, -7, -9, -25, and especially MMP2 and MMP12, degrade bovine and/or human MBP *in vitro* [147–152] (Fig. 5–1). A later study found that recombinant human MMP2, -7 and -9, but not MMP1, cleave recombinant human MAG *in vitro* (Fig. 5–2). Of the investigated MMPs, MMP7 degrades MAG most efficiently and also cleaves the extracellular portion of MAG off the cell membrane in a MAG transfected cell line [153].

MMP2 activity, and its expression by astrocytes, is increased three days after global cerebral hypoperfusion in C57BL6 mice. Repeated intraperitoneal administration of the broad-spectrum MMP inhibitor BB94 reduces the activity of MMP2 (and possibly of other MMPs) and decreases loss of MBP [154]. Moreover, MMP2 is highly expressed by foamy microglia and macrophages in MS lesions, especially at the border between plaque and normal-appearing white matter (NAWM), where it may contribute to the active demyelination of axons and/or the clearance of myelin debris [155].

Similarly, MMP12 may contribute to myelin damage in MS and after hypoxic-ischemic injury [156–159]. In MS, MMP12 is expressed in foamy microglia and macrophages in actively demyelinating lesions and the rim of chronic active lesions [156]. Theiler's murine encephalomyelitis (TME) is a virally induced MS model characterized by chronic brain inflammation and progressive demyelination. In the spinal cord of TME mice, MMP12 mRNA levels are markedly increased later on in the disease course [157]. In TME, oligodendrocytes as well as microglia/macrophages express MMP12 and in the spinal cord of TME-infected MMP12-/- mice, oligodendrocyte loss, demyelination and numbers of microglia/macrophages are reduced compared to wildtype mice [158]. Interestingly, the extent of BBB breakdown and global ECM deposition does not differ between $MMP12^{-/-}$ and wildtype mice [158]. However, direct stereotactic injection of activated MMP12 in the cerebellum induces recruitment of macrophages, oligodendrocyte death and loss of myelin, leading to the hypothesis that MMP12 plays a role in demyelination through its direct actions on oligodendrocytes and/or myelin and/or its role in macrophage extravasation [158]. Similarly, MMP12 mRNA and protein expression are markedly upregulated after experimental hypoxic-ischemic injury [159]. In the infarct area, MMP12 is expressed by neurons, microglia and oligodendrocytes. Treatment with a MMP12 short hairpin RNA reduced MMP12 protein expression, the extent of myelin damage and the infarct size [159]. Additionally, protein levels of MMP9 and the pro-inflammatory cytokine TNFα, which pro-form is a substrate for MMP12 [150], were decreased [159].

While there is a large body of evidence supporting the ability of MMPs to degrade myelin proteins, none of the aforementioned studies address the role of myelin degradation by MMPs in the context of disease, where MMPs may initiate or contribute to destruction of the myelin sheath or, alternatively, aid in creating a remyelination-permissive niche with the clearance of remyelination-inhibiting myelin debris [160]. Infection of astrocytes with human lymphotropic virus type I (HTLV1), the causative agent of the chronic demyelinating and neurodegenerative disease HTLV-associated myelopathy, upregulates MMP3 and -9 secretion, possibly initiating the destruction of the myelin sheath [161]. In a like manner, a study in a spontaneously demyelinating mouse model carrying extra copies of the DM20 gene, a myelin protein especially abundant during development, showed that MMP3 mRNA levels are highly upregulated prior to the onset of demyelination [162]. Crossing with TIMP1-overexpressing mice results in reduced (pro)MMP3 protein levels and ameliorates the clinical phenotype in about 50 % of the double transgenic offspring [162].

Interestingly, posttranscriptional modifications to MBP such as

citrullination, *i.e.*, conversion of arginine to citrulline groups, alters the electrical charge, the ability to form lipid vesicles and the degradability of MBP [163,164]. Levels of heavily citrullinated MBP are elevated in NAWM of MS patients [165] and this form of MBP is more readily degraded by MMP3 compared to its non-citrullinated counterpart [164] (Fig. 5–3). Moreover, non-citrullinated MBP from MS patients is more susceptible to cleavage by MMP3 than the same peptide from the brain of healthy controls [164], making it tempting to speculate that myelin from MS patients is more vulnerable to MMP3-mediated cleavage, which may play a role in the initiation, acceleration and/or exacerbation of myelin breakdown in MS.

6.3. MMP3 may trigger a microglia phenotype toxic to oligodendrocytes

Alternatively, MMP3 could initiate demyelination by giving rise to a microglia phenotype toxic to oligodendrocytes. Krabbe's disease is a rare but fatal demyelinating disease of childhood with a prevalence of about 1 in 100,000 [141]. The disorder is likely caused by mutations in the galactosylceramidase gene, which results in the accumulation of the intermediate lipid psychosine, and is pathologically characterized by the loss of myelin and oligodendrocytes and the presence of characteristic giant multinucleated microglia called 'globoid cells' [141]. Interestingly, mRNA expression of MMP3 is markedly elevated in a mouse model of Krabbe's disease [166]. Upon psychosine stimulation, primary mouse astrocytes, but not microglia, increase their expression of MMP3 mRNA [166]. In response to psychosine, primary mixed glial cultures give rise to highly phagocytotic globoid microglia and knockout of MMP3 completely abolishes the development of these globoid cells, indicating that astrocyte-derived MMP3 facilitates the transition of microglia into globoid cells [166]. Of note, coculture of psychosine-stimulated globoid microglia with oligodendrocytes actually results in less toxicity to oligodendrocytes than cocultures with control microglia [167]. However, when microglia are cultured in the presence of psychosine and tenascin C, an ECM protein elevated in Krabbe's disease, they become highly toxic to oligodendrocytes [167] (Fig. 5–4). Globoid microglia are also observed in other neurological disorders, such as amyotrophic lateral sclerosis, and may constitute a (failing) protective response or, alternatively, initiate or contribute to demyelination. The latter hypothesis is supported by the observation that active MMP3 secreted by dying PC12 neuronal cells polarizes primary mouse microglia towards a pro-inflammatory and neurotoxic phenotype [168]. A different study into spinal cord injury showed that endothelial cell-derived MMP3 activates BV2 microglia *in vitro* [169]. Moreover, MMP3-/- mice exhibit reduced microglial activation and oligodendrocyte death following spinal cord trauma, while treatment of wildtype mice with MMP3 shRNA-treated mice decreases microglial activation and oligodendrocyte death [169].

7. The effects of MMPs on oligodendrocyte lineage cell behavior during remyelination (failure)

7.1. Remyelination in health and disease

The brain's natural reaction to a demyelinating injury will be an attempt to restore the damage, which involves remyelination, *i.e.*, the formation of new myelin membranes around the denuded axons. In experimental rodent models, analogous to developmental myelination, the remyelination process roughly consists of two phases, being 1) activation, attraction and proliferation of adjacent OPCs and 2) differentiation of OPCs into remyelinating oligodendrocytes [9]. Recently it has become apparent that in MS lesions surviving mature oligodendrocytes may contribute to remyelination [7,8]. In adulthood, OPCs are present throughout the CNS and in addition reside in the subventricular zone of the brain [9]. In response to demyelination, signaling molecules are transiently expressed that activate these OPCs and recruit them to the damaged area [9]. As with most CNS injuries, microglia are the first responders to a demyelinating insult. Initially, these microglia (and peripheral macrophages) exhibit a more pro-inflammatory phenotype. They secrete inflammatory cytokines, such as IL1β and TNFα, to mobilize adjacent OPCs and astrocytes, as well as proteases to aid with the removal of myelin debris, which is a prerequisite for successful remyelination [160]. In animal models of robust remyelination, the pro-inflammatory microglia/macrophages then die by a form of programmed cell death called necroptosis, leaving the lesion to be repopulated by residual resident microglia with an anti-inflammatory phenotype [170]. Failure of this repopulation likely contributes to remyelination failure in chronic inflammatory conditions, such as MS and ageing [171]. Quickly after the microglia/macrophages have become activated, astrocytes will also respond to the primary insult and to soluble factors secreted by OPCs and microglia/macrophages. In addition to inflammatory cytokines, astrocytes transiently produce ECM proteins, such as fibronectin, hyaluronan and CSPGs, which inhibit oligodendrocyte maturation [129]. Ongoing inflammation may lead to the overactivation of astrocytes and the formation of an astrocytic scar that is impenetrable for OPCs, ultimately resulting in remyelination failure [172]. For successful remyelination, the OPCs need to be able to reach the demyelinated site and then receive the appropriate signals to differentiate into oligodendrocytes and remyelinate the denuded axons. MMP activity is likely required for effective remyelination, while dysregulation, either in the expression, localization or activity of MMPs, contributes to remyelination failure [34].

7.2. MMP activity is necessary for efficient remyelination

Under homeostatic conditions, the adult brain is relatively devoid of fibrous ECM glycoproteins, but upon demyelinating injury, the extracellular landscape drastically changes as a result of transient synthesis of ECM components, especially by astrocytes, such as hyaluronan, CSPGs, vitronectin, fibronectin and basement membrane proteins [15,173]. In concert, MMP expression, which is generally low in the adult CNS, is markedly upregulated, mainly by microglia, to facilitate the degradation of old and newly synthesized ECM components. Both the initial production of ECM (and other) proteins and their timely degradation by MMPs are essential for the recruitment of OPCs to the lesion and their subsequent differentiation into remyelinating oligodendrocytes. In the cuprizone model, mice are fed with a diet containing the copper chelator cuprizone. This compound is toxic to oligodendrocytes and induces reproducible demyelination, which is most pronounced in the corpus callosum [174,175]. When, after approximately 5 weeks, the mice are changed to a normal diet, the demyelinated areas are remyelinated within 2 weeks, making this a useful model to study successful remyelination. In the remyelination phase of the cuprizone model, mRNA levels of MMP3, -11, -12 and -14 are upregulated, while MMP24 mRNA expression is decreased [146]. Murine astrocytes and microglia upregulate their expression of MMP3 during remyelination [146,176,177]. Here, MMP3 may activate other MMPs, *e.g.*, MMP7 [28], by cleaving off their prodomain (Fig. 6A-1) and/or may cleave IGFBPs to release active IGF [96] (Fig. 6A-2). IGF is upregulated upon cuprizone-induced demyelination [175] and promotes remyelination by enhancing OPC survival and recruitment [178].

Although mRNA and protein levels of MMP7 levels are not changed in the corpus callosum 2 weeks after cessation of a cuprizone diet, when remyelination is almost completed [177], MMP7 expression is increased during early remyelination in the lysolecithin model [177]. Injection of the phospholipid lysolecithin in the spinal cord induces a demyelinating lesion, which spontaneously repairs within 21 days. Upon demyelination, astrocytes transiently upregulate fibronectin to stimulate proliferation of adjacent OPCs [21,22,179–181]. As fibronectin inhibits OPC differentiation *in vivo* [21], fibronectin levels need to decline in the remyelination phase and this decrease coincides with increased expression of MMP7 by microglia and macrophages [177]. In culture, rat microglia and macrophages secrete MMP7 in

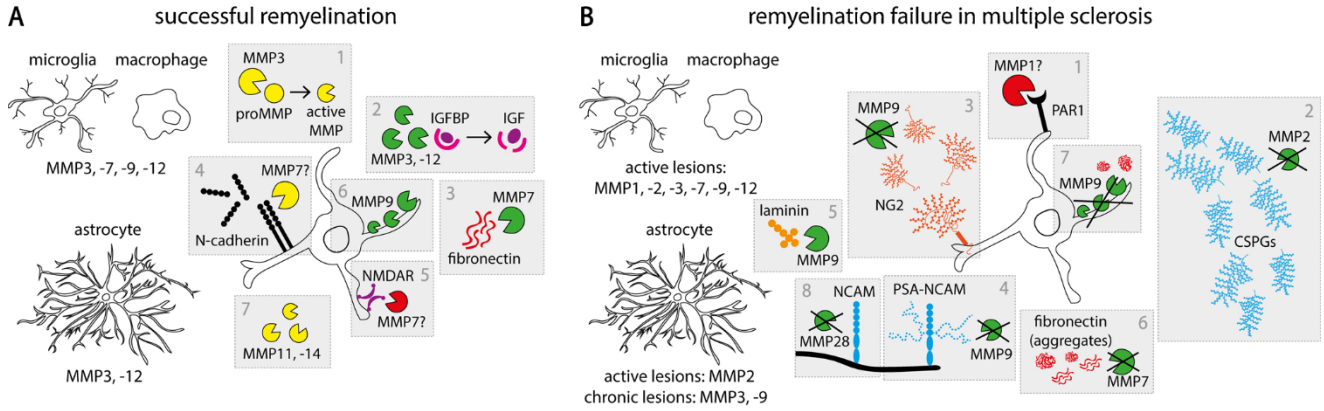

Fig. 6. The role of MMPs in successful remyelination and remyelination failure inmultiple sclerosis. A. Successful remyelination. **B.** Remyelination failure in multiple sclerosis. Matrix metalloproteinases (MMPs) are depicted in green when they have a positive effect on the behavior of the cell in question, in red for a negative effect and in yellow if the effect is yet unknown. When the effect of an MMP on a substrate is known, but this effect has not been directly demonstrated in the context of the oligodendrocyte lineage, a question mark is added, *e.g.*, 'MMP1?'. CSPGs - chondroitin sulfate proteoglycans; IGF - insulin-like growth factor; IGFBP - IGF-binding protein; NCAM - neural cell adhesion molecule; NG2 - neuron-glial antigen 2; NMDAR - *N*-methyl-D-aspartate receptor; PAR1 - protease-activated receptor 1; PSA-NCAM - polysialylated NCAM. See text for details.

response to anti-inflammatory, but not pro-inflammatory stimuli, and recombinant MMP7 efficiently degrades fibronectin *in vitro*. Moreover, factors present in the medium of the anti-inflammatory microglia/macrophages, degrade fibronectin after APMA-mediated activation of MMP-activity [177]. Thus, microglia/macrophage-derived MMP7 is likely responsible for the removal of OPC differentiation-inhibiting fibronectin, facilitating efficient remyelination (Fig. 6A-3).

In addition to fibronectin, MMP7 cleaves the adhesion protein N-cadherin, which is upregulated by astrocytes and especially oligodendrocytes in inactive and early remyelinating lesions in experimental autoimmune encephalitis (EAE), an MS animal model [182]. In analogy with developmental myelination, MMP7-mediated cleavage of N-cadherin may favor OPC recruitment at the early remyelination phase, while inhibiting myelination (Fig. 6A-4). In addition, the soluble full-length ectodomain of N-cadherin stimulates microglial activation and their secretion of pro-inflammatory factors, such as TNFα and MMP9 [88]. Although oligodendrocytes require endogenous membrane-associated MMP9 for proper process extension [112], the effects of extracellularly provided MMP9 on oligodendrocytes are unknown. Thus, MMP7-mediated shedding of N-cadherin in demyelinated lesions may alter the phenotype of microglia/macrophages. Moreover, MMP7 also cleaves NMDA receptors [36] (Fig. 6A-5). Blockade of NDMA receptors reduces oligodendrocyte maturation *in vitro* and delays remyelination *in vivo* in the cuprizone model [183]. Hence, due to its many substrates, MMP7 may have both positive and negative effects on remyelination.

Similarly, MMP9 mRNA levels are not changed during remyelination in the cuprizone model [146]. Nevertheless, MMP9 is expressed by oligodendrocytes in the mouse corpus callosum following lysolecithin-induced demyelination [184], where it may facilitate oligodendrocyte process extension [48,112,126] (Fig. 6A-6). Contrastingly, MMP12 is highly expressed in the cuprizone model, both in the demyelination phase, mainly by microglia, and in the remyelination phase, especially by astrocytes and oligodendrocytes [146]. MMP12 is known to cleave MBP [150] as well as IGFBPs [48], and promotes morphological oligodendrocyte differentiation [48] (Fig. 6A-2), therefore the increased expression of MMP12 is likely beneficial for oligodendrocyte lineage commitment and remyelination. However, functional studies, *e.g.*, with conditional knockout of MMP12 in the different glia cells still need to be performed to verify the importance of endogenous and extracellular MMP12 for remyelination.

Lastly, although validation at the protein level remains to be determined, the increase in MMP14 mRNA in the remyelinating cortex and corpus callosum, may contribute to the recruitment of OPCs, as MMP14 is implicated in the migration of OPCs on myelin tracts [75], possibly by cleaving NG2 [79]. Although MMP11 and MMP24 mRNA levels are respectively up- and downregulated during remyelination in the cuprizone model, little is known about the cellular source and CNS substrates of these MMPs nor about their functional roles in the developing or injured CNS (Fig. 6A-7). Overall, a comprehensive overview of the changes in MMP *protein* levels, as well as their function, in remyelination is still lacking. The few available studies are complicated by the time-sensitivity of changes in MMP expression, as many MMPs may only be needed for a short period of time, *e.g.*, during the switch from a myelination-inhibiting to a myelination-permissive environment [170]. Moreover, expression levels of ECM remodeling-related proteins like MMPs are relatively low compared to intracellular proteins, and thus changes in MMP levels are easily lost in large-scale proteomics analyses. On the other hand, functional studies are complicated by the large redundancy of MMPs with regards to substrate-specificity (see also Table 1). In MMP knockout models, compensatory upregulation of other MMPs may obscure effects of individual MMPs, for example loss of MMP9 or MMP12 only leads to a delay, but not a deficiency, in developmental myelination [48]. Ideally, an in-depth investigation should be performed, comparing expression of all known MMPs in experimental models of both efficient and inefficient remyelination.

7.3. Dysregulation of MMP activity contributes to remyelination failure in multiple sclerosis

With a prevalence of approximately 1 in 1000 individuals, MS is the most common demyelinating disease of the CNS [143]. In most patients, MS symptoms initially appear and disappear in a relapsing-remitting pattern as the demyelinated areas are remyelinated by oligodendrocytes [143]. Unfortunately, the remyelination process eventually fails, leading to the accumulation of irreversible disability [185]. For the progressive phase of MS there are only few disease-modifying drugs available, which still have limited efficacy. Although many ECM components promote the recruitment of OPCs, overproduction or failure of timely clearance of certain ECM molecules by MMPs is detrimental for OPC differentiation and remyelination. A recent study illustrated this by showing that the composition of brain ECM changes with ageing, increasing its rigidity, which inhibits remyelination by OPCs [186]. Similarly, the tissue composition of chronic demyelinated MS lesions is stiff compared to the surrounding NAWM, while actively demyelinating lesions are relatively soft [187]. Feeding mice with a cuprizone-containing diet for 6 weeks results in acute demyelination of the corpus callosum and an initial decrease in tissue stiffness, which recovers to normal values once remyelination has taken place [187]. However,

administering cuprizone for 12 weeks produces chronic demyelination, characterized by increased rigidity and more fibronectin deposition [187]. *In vitro*, stiff substrates markedly decrease the proliferation and differentiation of OPCs [186,188]. Thus, an alteration of the composition of the CNS ECM, caused by dysregulated ECM remodeling, contributes to remyelination failure. Indeed, chronically demyelinated MS lesions are characterized by increased deposition of fibronectin (aggregates), osteopontin and hyaluronan [21,129,189–191], while levels of CSPGs are decreased [192]. Although MMP1, -2, -3, -7, -9, -12 and -19 protein levels are increased in actively demyelinating MS lesions, little MMP expression is detected in chronic plaques [155,156,177,193–197].

Cleavage of many MMP substrates, including the cell surface proteins PAR1 (MMP1), N-cadherin (MMP7), NMDA receptors (MMP7), PSA-NCAM (MMP9) and NCAM (MMP28) are likely involved in both developmental myelination and remyelination. MMP1 is expressed by microglia-like cells in control white matter as well as by macrophage-like cells in active demyelinating MS lesions [193]. As cleavage of the PAR1 receptor by MMP1 increases NPC proliferation, but decreases differentiation to OPCs [57,58], upregulation of MMP1 in demyelinating lesions may contribute to failure of remyelination by reducing the numbers of OPCs and possibly myelinating oligodendrocytes (Fig. 6B-1).

A lack of MMP2 has been implicated in the accumulation of remyelination-inhibiting CSPGs after spinal cord injury [87,198–200]. CSPGs are a family of ECM proteins, including aggrecan, brevican, versican, neurocan, and the membrane-spanning NG2, that are well known to inhibit remyelination [16,26]. In the center of actively demyelinating MS lesions, ECM pattern staining of versican, aggrecan and neurocan is reduced and here the presence of CSPGs is highly increased in foamy microglia/macrophages [192]. At the edges of active lesions, CSPGs are localized in reactive astrocytes, while in chronically demyelinated lesions CSPGs are absent. In experimental animal models, different CSPGs are expressed depending on the type, location and severity of the injury [26,201,202]. More severe injuries, such as a stab injury to the spinal cord [202], lead to the formation of a chronic astrocytic scar containing CSPGs. Contrastingly, following lysolecithin-induced demyelination of the rat spinal cord, CSPGs are only transiently upregulated by microglia/macrophages in the lesion center and by astrocytes at the edges of the lesion [26]. *In vitro*, CSPGs negatively affect the migration, adhesion and differentiation of OPCs [24–27,87,203], while inhibition of CSPG synthesis *in vivo* accelerates remyelination in the lysolecithin [26,27] and cuprizone model [204]. A number of recombinant MMPs, most prominently MMP2 [205,206] and -3 [206], are able to degrade CSPGs *in vitro*. In response to traumatic injury of the mouse spinal cord, MMP2 activity is upregulated by reactive astrocytes, especially at the border between lesion and uninjured tissue, where its expression colocalizes with CSPGs [198,199]. Total knockout of MMP2 leads to increased accumulation of CSPGs, a more extensive astrocytic scar, more severe myelin damage and higher residual disability 42 days after the initial spinal cord injury [199]. In line with this, transplantation of umbilical cord-derived mesenchymal stem cells 7 days after spinal cord injury increases MMP2 activity and MMP2 expression by neuronal cells, while decreasing CSPG accumulation and scarring [200]. In addition to astrocytes [199] and neurons [207], OPCs also secrete MMP2 [87]. Addition of the synthetic peptide Intracellular Sigma Peptide (ISP) to OPC cultures enhances their secretion of active MMP2, enabling the OPCs to better migrate over a CSPG-rich barrier [87]. Furthermore, in the EAE and lysolecithin animal models, ISP treatment also promotes MMP2 secretion by OPCs, leading to increased degradation of CSPGs and enhanced remyelination [87]. Even so, in actively demyelinating MS lesions, MMP2 expression is readily observed in astrocytes as well as foamy microglia/macrophages, raising the question why remyelination still often fails in MS. Conceivably, levels of secreted MMP2 and/or active MMP2 may be insufficient for the timely removal of CSPGs. Alternatively, as CSPGs are not part of the astrocytic scar in chronically demyelinated MS lesions, implying their successful removal (likely by MMP2), CSPGs may not play as an important role in MS as they do in spinal cord injury, where they prevent functional recovery by inhibiting OPC differentiation as well as axonal outgrowth [208]. More research is required to assess the benefits of CSPG-targeting therapies in animal models of failed remyelination, such as chronic cuprizone treatment. In conclusion, remyelination-inhibiting CSPGs are upregulated in response to (demyelinating) injuries, where they may contribute to the formation of a chronic astrocytic scar (Fig. 6B-2). In the demyelinated areas, secretion of MMP2 by OPCs, astrocytes, neurons and possibly microglia/macrophages, enhances CSPG degradation, enabling OPC migration, differentiation and ultimately remyelination. Thus, enhancing the expression of MMP2 in demyelinating diseases, such as spinal cord injury and possibly MS, may be a promising therapy to enhance remyelination.

MMP2 is not the only gelatinase that has been implicated in the degradation of CSPGs. To prevent its accumulation in the ECM, MMP9 degrades the membrane-spanning CSPG NG2 after it has been shed from the surface of OPCs by other proteases [79,209] (Fig. 6B-3). *In vitro*, plating of cells on an NG2 matrix reduces the morphological differentiation of rat OPCs, but not of mouse OPCs [210]. Following lysolecithin-induced demyelination in wildtype mice, NG2 proteins are cleaved from the surface of OPCs by ADAM8 and -10 [79,209] and initially accumulate in the extracellular environment of the lesion [210]. Then, MMP9-expressing microglia/macrophages appear and two weeks after the initial insult NG2 is cleared and the lesion efficiently remyelinated [210]. However, in total MMP9$^{-/-}$ mice NG2 persists and remyelination is reduced [210], suggesting a role for microglia/macrophage-derived MMP9 in the removal of oligodendrocyte maturation-inhibiting NG2. Indeed, MMP9 expression is observed in foamy microglia/macrophages in actively demyelinating lesions, but not in chronically demyelinated lesions, where it is found in astrocytes [193–196]. In support of a role of extracellular MMP9 in remyelination, MMP9 has been identified as one of the remyelination-promoting factors in DUOC-01, a therapeutic candidate for demyelinating diseases, which contains human umbilical cord-derived monocytes and increases remyelination in the cuprizone model [211]. Here, MMP9 may positively influence remyelination by degrading extracellular NG2 (Fig. 6B-3) and/or by cleaving PSA-NCAM from neuronal axons [124] (Fig. 6B-4). Intriguingly, PSA-NCAM is re-expressed on neuronal axons in chronically demyelinated MS lesions, but is not present on remyelinated axons in shadow plaques [212], suggesting a role in the negative regulation of OPC differentiation similar to developmental myelination. Although MMP9 is present in hypertrophic astrocytes in chronic MS lesions, it is unknown whether astrocytes secrete MMP9 and/or whether MMP9 is active. Moreover, in the same lesion, astrocyte-derived MMP9 may not have the same effects as microglia-derived MMP9. For example, mislocalization or a lack of secretion of cofactors may hinder the efficacy of MMP9, making it tempting to speculate that a lack of PSA-NCAM cleavage by secreted (active) MMP9 in chronic MS lesions contributes to remyelination failure. Contrastingly, a study into spinal cord injury, actually showed a positive effect of short-term MMP9 (and possibly MMP2) inhibition on remyelination [213]. Following spinal cord hemisection, repeated administration of the gelatinase inhibitor SB-3CT led to increased proliferation of NG2-positive cells, enhanced remyelination and better functional recovery [213]. Although, it remained unclear whether the milder disease course was due to increased expansion of OPCs and their differentiation in myelinating oligodendrocytes or merely the consequence of reduced MMP-mediated BBB breakdown leading to less inflammatory demyelination [213]. Even so, cleavage of remyelination-inhibiting proteins like NG2 and PSA-NCAM are likely not the only actions of MMP9 in demyelinating areas. In addition, MMP9 has been implicated in the degradation of laminin [214], an ECM protein known to positively influence oligodendrocyte differentiation [19,64,65,138,139]. In EAE lesions, MMP9 activity colocalizes with laminin degradation. Moreover, administration of

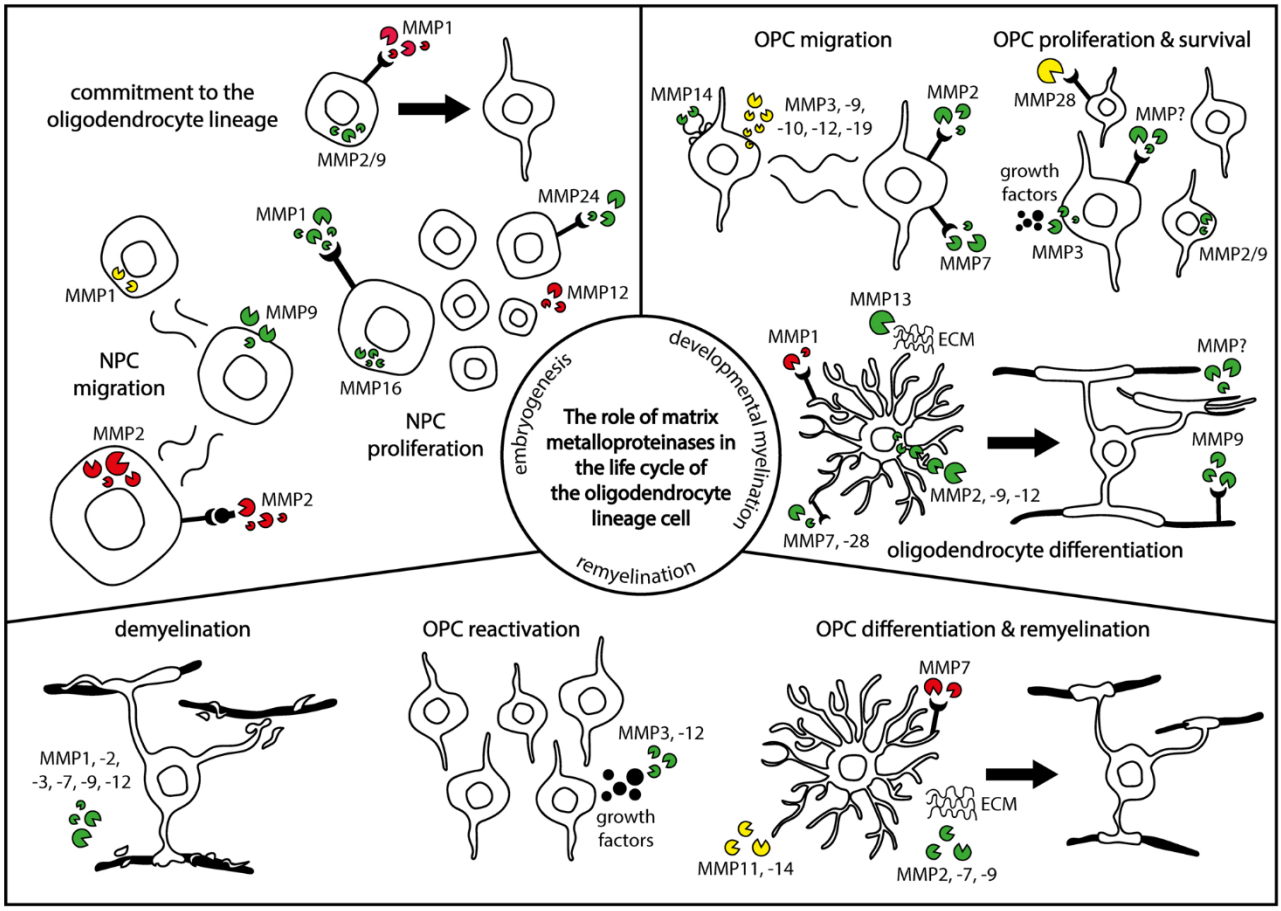

Fig. 7. The role of MMPs in the life cycle of the oligodendrocyte lineage cell. Left panel: Neural progenitor cell (NPC) migration, proliferation and commitment to the oligodendrocyte lineage. Right panel: Oligodendrocyte progenitor cell (OPC) migration, proliferation and differentiation to a myelinating oligodendrocyte. Bottom panel: Demyelination, OPC reactivation and oligodendrocyte differentiation and remyelination. Matrix metalloproteinases (MMPs) are depicted in green when they have a positive effect on the behavior of the cell in question, in red for a negative effect and in yellow if the effect is yet unknown. If the effect on a substrate is known, but the protease in question has not yet been identified, this is written as 'MMP?'. When the effect of an MMP on a substrate is known, but this effect has not been directly demonstrated in the context of the oligodendrocyte lineage, a question mark is added, *e.g.*, 'MMP1?'. See Figs. 2–6 and text for details.

berberine, a plant derivative used in traditional Chinese medicine, reduces MMP9 activity and laminin degradation. This makes it tempting to speculate that upregulation of MMP9 expression in response to demyelination leads to undesired degradation of laminin, negatively affecting oligodendrocyte differentiation [214] (Fig. 6B-5).

Although MMP3 is occasionally observed in foamy microglia/macrophages in actively demyelinating and remyelinating MS lesions, its expression is especially prominent in hypertrophic astrocytes in chronic plaques [177,193]. As MMP3 can activate other MMPs by cleaving off their prodomain [28,29,215], its increased expression might be an attempt to compensate for low levels of other MMPs, *e.g.*, MMP7. We have recently linked the formation of remyelination-inhibiting fibronectin aggregates in chronic MS lesions to decreased expression of MMP7 [177]. Although foamy microglia/macrophages express MMP7 in actively demyelinating MS lesions, MMP7 is hardly present in chronic (in) active MS lesions, correlating with the persistence of fibronectin aggregates [177]. This has led us to hypothesize that the intermediate phenotype microglia/macrophages present in MS lesions [216] provide insufficient MMP7, leading to accumulation of fibronectin and ultimately the formation of OPC-inhibiting fibronectin aggregates [177] (Fig. 6B-6). Possible mechanisms by which accumulated fibronectin (aggregates) inhibit oligodendrocyte process outgrowth is through mislocalization of MMP9 activity [126] (Fig. 6B-7), disturbed vesicle transport to myelin membranes [217] and incorrect formation of membrane microdomains [218–220].

Similar to cuprizone-induced demyelination, MMP12 is highly expressed by foamy microglia/macrophages in actively demyelinating MS lesions [156]. Here, it may cleave myelin proteins, but also IGFBPs to increase the bioavailability of IGF to OPCs in analogy to developmental myelination [96]. Lastly, protein levels of (pro)MMP28 are increased in the cortex of MS patients compared to healthy controls [104]. Moreover, examination of spinal cords of mice with EAE and the cerebellum of one MS patient revealed that MMP28 expression is highly upregulated in neuronal axons in demyelinated areas [104]. Thus, in demyelinated areas, the upregulation of MMP28 may decrease OPC numbers *via* degradation of NCAM receptors [103], contributing to remyelination failure in MS (Fig. 6B-8).

To conclude, during robust remyelination in experimental models a number of MMPs, most prominently MMP3, -7, -9 and -12, are transiently expressed in the CNS. These MMPs work together to degrade OPC-inhibiting ECM proteins, release IGF and cleave cell surface proteins, collectively shaping a remyelination-permissive environment in the oligodendrocyte niche. Additionally, like in developmental myelination, endogenous MMP9 in oligodendrocytes may facilitate process extension. However, in demyelinating disorders, chronic inflammation or other disease-specific factors can trigger an overabundance or a shortage of certain MMPs, which leads to the accumulation of prohibitive factors in the oligodendrocyte niche, contributing to remyelination failure in MS lesions.

8. Conclusions and future perspectives

In summary, MMPs are highly, but transiently, upregulated during brain development and upon demyelinating injury, and influence the behavior of oligodendrocyte lineage cells throughout their life cycle (summarized in Fig. 7). Many actions of MMPs, *e.g.*, cleavage of IGFBPs by MMP3 and -12, affect oligodendrocyte lineage cells at multiple stages of their development. Early on in brain development, MMP1 increases NPC proliferation, but decreases commitment of NPCs to the oligodendrocyte lineage by cleaving SFD1α and PAR1. Later on, distinct MMPs influence the migration, proliferation and survival of OPCs by cleaving cell surface receptors, such as dystroglycan and NCAM, and by releasing active IGF1 from IGFBPs. Subsequently, endogenous expression of MMP9 plays an important role in oligodendrocyte differentiation by facilitating oligodendrocyte process extension. Moreover, near the completion of developmental myelination, MMPs are needed to clear ECM proteins that inhibit OPC differentiation. In the event of demyelination, a number of these MMPs are transiently expressed and may play a role in the initiation and/or exacerbation of demyelination by degrading myelin proteins (*e.g.*, MMP2 and -12) or by initiating oligodendrocyte death (MMP3). Finally, MMPs, including MMP2 and -7, are likely implicated in remyelination by cleaving a multitude of cell surface proteins and especially by clearing remyelination-inhibiting ECM proteins.

Thus, MMPs are versatile and powerful enzymes that affect oligodendrocyte lineage cells in all stages of development by clearing ECM components and cleaving a wide spectrum of other proteins. The activity of MMPs needs to be tightly regulated, as both upregulation and a lack of MMPs can be detrimental and play a role in pathological conditions characterized by demyelination and/or failure of (re)myelination. Indeed, a non-permissive niche for OPC differentiation, by means of an aberrant expression and/or function of many MMP substrates, including ECM proteins, cell surface molecules and growth factors, is implicated in remyelination failure. Given their dysregulated expression in chronically demyelinated MS lesions, MMPs may fail to shape the oligodendrocyte niche into a remyelination-promoting environment. For now, there is still a lack of evidence demonstrating a causal relationship between dysregulation of MMPs, the accumulation, abnormal degradation and/or lack of shedding of MMP substrates and alterations in oligodendrocyte lineage cell behavior. Investigations are often complicated by the large redundancy of MMPs *in vivo*, which obscures the effects of individual MMPs in experimental knockout models. Moreover, a focus on animal models has obscured the potential remyelinating capacity of mature oligodendrocytes in MS lesions, leaving many questions on how MMPs substrates, including ECM proteins, growth factors and adhesion molecules, may affect myelin biogenesis by mature oligodendrocytes. In addition, we need to remain aware that both MMP substrates, including ECM proteins, and MMPs are differentially expressed throughout the CNS. Therefore, lessons learned about MMP activity in oligodendrocyte lineage cells in the white matter or brain may not apply to the grey matter or spinal cord. A wide and in-depth investigation is needed to evaluate MMP protein expression, and especially activity, in different CNS regions during development, demyelination and remyelination (failure).

More clarity on the pathological actions of MMPs on oligodendrocyte lineage cell behavior in the different stages of the life cycle is needed to target remyelination failure in a specific and effective manner. For over thirty years, numerous MMP inhibitors have been tried (and mostly failed) as therapeutic agents in a wide range of diseases, including cancer, rheumatoid arthritis, ulcerative colitis, diabetes and MS [221]. In the late nineties, clinical trials investigating the first generation of MMP inhibitors were complicated by significant side effects, such as musculoskeletal symptoms and inflammation, due to the ubiquitous expression of MMPs and the lack of specificity of the MMP inhibitors [221]. Later drug candidates were found to be more specific and led to fewer side effects, but often lacked efficacy [221]. To date, only one MMP inhibitor has been approved by the American Food and Drug Administration, namely doxycycline, which is an antibiotic that at a low dose acts as a broad-spectrum MMP inhibitor [222]. Doxycycline is registered as a treatment for periodontitis [222], but interestingly its anti-inflammatory actions may also provide therapeutic benefit as an add-on therapy in MS [223,224]. Furthermore, recent technological advances in pharmaceutical development are leading to a new generation of highly specific MMP inhibitors [225]. X-ray crystallography has revealed the 3D structure of MMPs, while computer simulations can be used to predict the interactions of MMP binding sites with candidate molecules [221]. High-throughput drug screenings, *e.g.*, employing existing libraries of compounds, enable researchers to quickly test the binding capacity of a large number of drugs to their MMP of interest [221,226]. Furthermore, monoclonal antibodies against specific MMPs are increasingly being developed and the first clinical trials testing a monoclonal antibody against an MMP have already been performed [221]. So far, *Andecaliximab*, a monoclonal antibody against MMP9, is found to be safe and well-tolerated in patients, but without therapeutic benefit over placebo in ulcerative colitis [227] and Crohn's disease [228], while phase II clinical trials for advanced gastric cancer [229] and rheumatoid arthritis [230] are still underway. Lastly, new methods of targeted drug-delivery, such as nanoparticles or exosomes, could be employed to increase the efficacy of MMP inhibitors by enabling them to cross over the BBB [231].

Together, these technological advances create exciting opportunities for the development of MMP inhibitors as treatments for a wide range of (inflammatory) diseases. Such MMP-specific, and possibly tissue-specific, drugs are especially promising in conditions such as Krabbe's disease, where the upregulation of one MMP, *i.e.* MMP3, plays a clear causal role in the development of the disease. In multifactorial diseases, such as MS, where multiple MMPs are simultaneously at play, the use of MMP inhibitors may be more complex. On the one hand, MMP inhibitors could be used to promote remyelination in MS by decreasing the activation and release of proinflammatory factors by MMPs in the circulation and/or the brain. Alternatively, MMP inhibitors, or promotors, could target the dysregulated expression of specific MMPs known to influence oligodendrocyte lineage cell behavior. For example, inhibition of MMP1 may promote remyelination by decreasing PAR1 activation and increasing oligodendrocyte lineage commitment and myelination. Whilst increasing MMP2 or MMP7 activity could promote remyelination through clearance of remyelination-inhibiting substrates, *i.e.* CSPGs by MMP2 and fibronectin (aggregates) by MMP7. However, for efficient remyelination, many MMPs need to be expressed in a time-dependent manner. Badly timed inhibition or promotion of MMPs could actually be detrimental to remyelination, *e.g.*, by hampering the clearance of myelin proteins or by degrading remyelination-promoting factors. Therefore, 'smart' MMP inhibitors and promotors need to be developed that perform their actions at the right time and place. In conclusion, MMPs are interesting targets for the development of new remyelination-promoting pharmaceuticals. More knowledge on the role of MMPs in shaping the oligodendrocyte niche may ultimately contribute to the development of remyelinating strategies for devastating demyelinating disorders such as MS and Krabbe's disease.

Author contributions

Both authors contributed to the conception of the manuscript; RPG performed the literature search, data analysis and drafted the manuscript; WB critically revised the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgments

Work in the Baron Laboratory is supported by grants from the Dutch MS Research Foundation (Stichting MS Research). RPG is recipient of a Junior Scientific Masterclass MD/PhD fellowship of the University Medical Center Groningen.

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